

Original research

Hypertension potentiates cataractogenesis in rat eye through modulation of oxidative stress and electrolyte homeostasis

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Abstract

Purpose: To evaluate modes of cataractogenesis in the hypertensive state by using different hypertensive animal models, including fructose, cadmium chloride (CdCl_2), N_ω -nitro-L-arginine methyl ester (L-NAME), and two-kidney, one clip (2K1C) method.

Methods: Male Sprague–Dawley albino rats (150–180 g) were divided into different groups, each group containing six animals. Hypertension was induced in animals via six weeks administration of fructose (10% solution in drinking water), CdCl_2 (0.5 mg/kg/day, i.p.), and L-NAME (20 mg/kg/day, p.o.) in their respective groups and NaCl (0.9% solution in drinking water) in the 2K1C group. The Ramipril-treated group (2 mg/kg/day, orally) served as a standard group for the 2K1C animal model. Blood pressure was measured biweekly using non-invasive blood pressure system. The biochemical parameters in serum and eye lenses were evaluated after six weeks of the experimental protocol.

Results: Hypertensive animal models showed significant induction of systolic and diastolic blood pressure and modulation of oxidative stress through depletion of antioxidants, including glutathione peroxidase, catalase, superoxide dismutase, glutathione, and elevation of malondialdehyde in serum and eye lenses. A significant elevation of ionic contents (Na^+ and Ca^{2+}) and reduction of total protein and Ca^{2+} ATPase activity in eye lenses were observed in all hypertensive animal models except L-NAME when compared with the normal group. The significant restoration of the antioxidants, Malondialdehyde (MDA) total protein, and ionic contents in the eye lenses concomitant with reduction of blood pressure were observed in the ramipril-treated group as compared to the 2K1C animal model. The results indicate that the fructose, CdCl_2 , and 2K1C models showed pronounced cataractogenic effects in the rat eye lenses.

Conclusion: Based on our findings, it can be concluded that systemic hypertension significantly increases the risk of cataract formation in the rat eyes via modulation of the antioxidant defense mechanism and electrolyte homeostasis.

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Keywords: Hypertension; Cataract; Oxidative stress; Fructose; CdCl_2 ; Two-kidney, one clip

Introduction

Cataract is the leading cause of blindness in the world and the most prevalent ocular disease.¹ The number of cataract-

blind is expected to increase dramatically in coming decades as the number of elderly in the world's population increases. It is suggested that the number of cataract-blind could reach close to 40 million by the year 2025.² There are several risk factors which are associated with induction of cataractogenesis, such as diabetes, oxidative stress, ultraviolet radiation, age, etc.³ Several epidemiological studies revealed that hypertension is also associated with cataract, but sometimes it is significant^{1,4,5} and sometimes not.⁶ Their studies, however, lacked the exact exploitation of biological mechanism involved in the entire process regarding the exacerbation of cataract in hypertensive state. Some preclinical studies

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indicate that systemic hypertension may alter the electrolyte homeostasis through inhibition of $\text{Na}^+ \text{K}^+$ ATPase pump activity in the lens which causes the cataract formation,⁷ but at present, another possible mechanism involved in cataractogenesis through hypertension is still unclear. In this perspective, we designed an experimental study to evaluate modes of cataractogenesis in the hypertensive state by using different hypertensive animal models, such as fructose, cadmium chloride (CdCl_2), N_ω -nitro-L-arginine methyl ester (L-NAME), and two-kidney, one clip (2K1C), which have different modes of cellular pathogenesis. In fructose animal model, chronic fructose administration induces hypertension by systemic oxidative stress, sympathetic overactivity, and increased production of vasoconstrictor molecules, viz endothelin-I and angiotensin-II.⁸ CdCl_2 induced hypertension is related to Ca^{2+} mimicking contractile activity of cadmium ion on vascular smooth muscles,⁹ oxidative damage, and vascular endothelial dysfunction.¹⁰ The 2K1C model elevates the plasma renin activity, which activates the angiotensin II-mediated hypertensive actions,¹¹ and L-NAME modulates the nitric oxide (NO) level in smooth muscles, which lead to elevation of blood pressure.¹²

Methods

Drugs and chemicals

L-NAME was purchased from Sigma–Aldrich (St. Louis, MO, USA). D-fructose and CdCl_2 were purchased from HiMedia chemicals (Mumbai, India). Ramipril was obtained from Cipla Limited (Mumbai, India) as a gift sample. Other chemicals and reagents used were of analytical grade.

Experimental animals

Sprague–Dawley albino male rats (150–180 g) were used for the experimental study and were housed under standard environmental condition ($23 \pm 2^\circ\text{C}$, with $55 \pm 5\%$ humidity and 12 h light/dark cycle) according to the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Govt. of India, and were fed a standard pellet diet with water *ad libitum* under hygienic conditions. Animals were habituated to laboratory conditions for at least 48–72 h prior to the experimental protocol to minimize non-specific stress, if any. The protocol was approved by the Institutional Animal Ethics Committee (IAEC) of Institute of Pharmaceutical Science, Guru Ghasidas Vishwavidyalaya, Bilaspur (C.G), India (Reg. No.-994/GO/ERe/S/06/CPCSEA), and the experiments were conducted according to the ethical principles and guidelines provided by CPCSEA, Govt. of India and the Association for Research in Vision and Ophthalmology (ARVO) for animals.

Experimental design

Male Sprague–Dawley albino rats (150–180 g) which were normal regarding the ocular examination and blood

pressure at the baseline were randomly selected and divided into six different groups, each group containing six animals. Hypertension was induced in animals via six-week administration of fructose (10% solution in drinking water) in group II,¹³ CdCl_2 (0.5 mg/kg/day, i.p.) in group III,⁹ L-NAME (20 mg/kg/day, p.o.) in group IV¹⁴, and in group V, hypertension was induced by 2K1C animal model.¹⁵ The ramipril-treated group (2 mg/kg/day, p.o.) served as standard group (2K1C animal model).¹⁶ Group I served as normal control.

The systolic (SBP) and diastolic blood pressure (DBP) in each group were monitored biweekly via non-invasive blood pressure system (NIBP; CODA-08 Channel, Kent scientific, USA), and biochemical parameter in serum and eye lens were determined after six weeks in sacrificed animals.

Surgical procedure for 2K1C model

2K1C was performed on all the rats by anesthetizing with ketamine and xylazine (60:10 mg/kg, i.p.). The kidney was visualized by a left lateral abdominal incision, and the left renal artery and ureter were ligated by a silk thread. The muscle and skin layer (incision site) were sutured with highly sterile suture needles. After surgery, rats were allowed to drink water *ad libitum*, with no further treatment. All uninephrectomized animals were given 0.9% NaCl in the drinking water for six consecutive weeks.¹⁵

Blood collection

Animals were sacrificed after six weeks, blood was collected from each group via cardiac puncture, and serum was separated and stored at $2-8^\circ\text{C}$ for further biochemical analysis.

Preparation of lens homogenate

The eyeball was isolated from the sacrificed animals. Lenses were dissected via posterior approach, washed with cold saline, and stored with saline at -20°C until analysis. Lens homogenate was prepared from both lenses of each animal in 10 volumes of 0.1 M potassium phosphate buffer (pH 7). The homogenate was centrifuged at 10,000 rpm for 1 h, and the supernatant was separated and used for biochemical analysis.¹⁷

Determination of lenticular opacity

The lenticular opacity of the experimental groups was determined by the photographic method based on the appearance of graph lines through the lens. The eye lenses were dissected via a posterior approach, put on graph paper immediately, and photographed by a digital camera (Sony Cybershot DSC-W810). The graph lines would appear clearly in the transparent lens and cloudy or not visible in the cataractous lens.¹⁸

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